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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1642	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/684,890	Applicant(s) ZENTGRAF ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-12 are pending in the application and are currently under prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims because there is insufficient guidance and working exemplification in the specification commensurate in scope with the claims to enable one skilled in the art to practice the claimed method with a reasonable expectation of success without having to first perform extensive and undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

There is no working exemplification of the claimed method for diagnosing the existence of any and all types of malignant carcinoma and sarcoma in any and all mammals. There is no working exemplification of the claimed method for diagnosing the pathological developmental stage of any and all types of malignant carcinoma and sarcoma in any and all mammals. There is no working exemplification of the claimed method for diagnosing the grade of any and all types of malignant carcinoma and sarcoma in any and all mammals. In the absence of such exemplification one skilled in the art would not accept the assertion that the invention can be used effectively to diagnose the presence, stage, or grade of any carcinoma or sarcoma in any mammal.

Certainly, there is insufficient guidance and exemplification in the specification to enable one skilled in the art to use any body sample for diagnosis. For example, there is no factual evidence of record that suggests that the antigen is shed or secreted by tumor cells into the mammal's circulatory system; therefore, it is unlikely that one could successfully diagnose an ovarian carcinoma by determining the level of expression of Nup88 in the plasma.

Furthermore, there is no factual evidence of record that indicates that the level of Nup88 correlates with the onset, presence, or incidence of any type of carcinoma or sarcoma in any mammal. As such, there is no factual evidence of record that the invention can be used effectively in a clinical setting to diagnose the presence, stage, or grade of any carcinoma or sarcoma in any mammal.

Ward (*Developmental Oncology* **21**: 91-106, 1985) teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable (see abstract). Even CA-125, one of the more reliably used biomarkers known in the art, is not always effective for rendering a diagnosis of every type of cancer, particularly ovarian cancer (see US Patent No. 5,356,817-A; column 2, line 47 to column 3, line 2). Thus, the efficacy of using a particular tumor marker cannot be predicted by one skilled in the art and can only be determined empirically.

Furthermore, it is has become increasingly recognized in the art that the use of a single diagnostic biomarker of cancer may be ineffective, particularly for

the diagnosis of differently staged cancer. A newsletter published in 1997 by the Genesis Group Associates, Inc. (*Genesis Report-Dx*, Vol. 6, No. 3) teaches:

> "What we realize about tumors now is that they may not express that one marker you might be testing for, depending on the stage.
> "Over a period of time, as tumors become more aggressive, they express more tumor markers. But if you rely on a single marker you might not be able to detect that a tumor marker is actually being expressed" (NLDB Accession No. 97:320100, © 2001 Gale Group, page 5).

For example, with specific regard to the use of TIMP-1 as a marker, Oberg, et al (*Anticancer Research* **20**: 1085-1091, 2000) teach that analyses of the total concentration of TIMP-1 in serum samples acquired from colorectal patients reveal that TIMP-1 is of limited value for tumor staging and prognosis (abstract). Oberg, et al teach that "wide, overlapping ranges" of concentrations are observed, which serves to preclude the usefulness of analyses of TIMP-1 and other measured factors. It remains to be determined whether or not Nup88 expression levels can be used to distinguish malignant tissue from non-malignant tissue, but as the teachings of Oberg, et al indicate, it is critical that the range of expression of Nup88 in the malignant tissue not overlap significantly with the range of expression in the non-malignant control tissue, otherwise the level of Nup88 "over-expression" in malignant tissue will be of little diagnostic value.

Additionally, Pohl et al (non-serial, meeting abstract, 3rd International Conference of the Mediterranean Society of Tumor Marker Oncology, 1994) teach:

> No individual tumor marker is expressed by all histological types of ovarian cancer; accordingly, the combined use of several markers may help to overcome this diagnostic insensitivity. However, given the rapid growth in the number of tumor markers to choose from, there is a pressing need to objectively select those marker panels which are most meaningful and cost-effective in clinical practice.

Although Pohl, et al refers to ovarian cancer, the teachings are relevant to a consideration of any protein that might be used as a diagnostic marker of any type of cancer.

Even if Nup88 is determined to be suitable for use, the specific guidelines that might be used for analysis of the resultant data acquired by the measurement of the concentration of the antigen in a sample are absent from the specification. Tockman, et al (*Cancer Research* **52**: 2711s-2718s, 1992) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to diagnosis of any type of cancer, including colorectal and breast cancer. Tockman, et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end-points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (emphasis added) (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end-point marker (page 2714, column 1). Clearly, prior to the successful application of newly described markers, validation against acknowledged disease end-points must occur and the markers' predictive value must be confirmed in prospective population trials (page 2716, column 2).

In consideration of the need to first validate the use of Nup88 as a marker before its clinical application, it is noted that the increased expression of the antigen alone may not be pathologic. Therefore, the increased expression of antigen may not be diagnostic of any type of cancer of any stage or grade. It is

also possible that increased levels of the antigen are associated with late stage disease; in which case, the determination of the level of the antigen in a sample could not be used effectively to screen patients for the presence of early stage cancer.

In summary, particularly in view the unpredictability in the art of cancer diagnosis and staging, in the absence of sufficient guidance and working exemplification that is commensurate in scope with the claims, one skilled in the art cannot practice the claimed invention commensurate in scope with the claims with a reasonable expectation of success. Consequently, one skilled in the art would be forced to perform extensive and undue experimentation in order to practice the claimed method and therefore the specification fails to meet the enablement requirements of 35 USC § 112, first paragraph.

4. The specification is objected to and claims 6, 8, and 12 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

Claims 6 and 8 are drawn to a method for using a monoclonal antibody, which is designated 149/1/1 and which is produced by the hybridoma cell line having the DSM accession no. ACC 2457. Claim 12 is drawn to the monoclonal antibody.

It is unclear if a cell line that produces an antibody having the exact structural and chemical identity of the monoclonal antibody to which the claims refer is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing the monoclonal antibody to which the claims refer, it would not be possible to practice the claimed invention, because it would not be possible to make the monoclonal antibody. Therefore, a suitable deposit for patent purposes

is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics (Fundamental Immunology, 3rd ed., William E. Paul, M.D. ed., 1993, page 242). Therefore, it would require undue experimentation to reproduce the claimed antibody. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph (see 37 C.F.R. 1.801-1.809).

Applicant's referral to the deposit of the hybridoma cell line on page 5 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of MPEP 608.01 (p)(c) are met.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the

provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite because claim 1 recites the phrase "and/or" in lines 1 and 2. Recitation of the phrase renders the claim indefinite. For example, it cannot be ascertained whether the claimed method can be used to determine the existence of carcinomas or just sarcomas or both carcinomas and sarcomas. Similarly, it cannot be ascertained whether the claimed method can be used to determine the existence of or only the stage or grade of a malignancy or alternatively both. Also, it is unclear whether the claimed method can be used to determine the stage and grade of a malignancy or both. Accordingly, one of

ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 1-11 are indefinite because claims 1-8 recite the phrase "characterized by" or "characterized in that". In regard to claim 1, recitation of the phrase renders the claim indefinite because it is unclear what is to be characterized by the preparation. Moreover, assuming that the claimed method is to be characterized by the preparation, it is unclear how the method is to be characterized by the preparation. With regard to claims 2-8, recitation of the phrase renders the claims indefinite because it is unclear how and to what extent the method is to be characterized by the recitation that follows "characterized". Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 1-11 are indefinite because claim 1 recites the term "overexpression". According to the specification, the term "overexpression" means, "**more** protein Nup88 can be found in the body sample than in healthy controlled tissue" (emphasis added) (page 4, lines 24-26). Therefore, the term "overexpression" is a relative term. Because the specification does not provide a standard for ascertaining the requisite degree of overexpression, recitation of the term renders the claim indefinite and therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Amending claim 1 to recite, for example, the phrase "wherein said carcinomas or sarcomas express more than three times the level of Nup88 as compared to normal cells of the same tissue type" might obviate this rejection. However, Applicant is cautioned against the introduction of new matter by amendment.

Claims 1-11 are indefinite because claims 1, 3-5, and 9-11 recite the designation "Nup88" as the sole means of identifying the polypeptide to which the claims refer. The use of laboratory designations only to identify a particular polypeptide renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides. Amendment of the claims to include the amino acid sequence of the polypeptide

by reference to a specific sequence identification number, which corresponds to the matching amino acid sequence in the Sequence Listing, can obviate this rejection, because the amino acid sequence of a polypeptide is unique identifier that unambiguously defines a given polypeptide.

Claims 1-11 are indefinite because claim 1 does not recite a positive process step that clearly relates back to the preamble of the claim. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Amending claim 1 to recite, for example, the phrase "whereby the diagnosis of the existence of the malignancy of carcinoma in said mammal is made" at the end of the last line of the claim might obviate this rejection.

Claim 7 and 8 are indefinite because claim 7 recites the term "homology". It is unclear if the term is meant to connote sequence homology, structural homology, or functional homology. Furthermore, the term "homology" is a relative term, but the term is not defined in the specification nor does it provide a standard for ascertaining the requisite degree to which the proteins must be homologous. Accordingly, it is unclear if the claims require the proteins to be identical or merely similar in sequence, structure, or function. Because the degree of homology exhibited one protein relative to another can range from the absence of identity or similarity to complete identity or similarity, recitation of the term renders the claim indefinite. Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 8 is indefinite because the claim recites the term "virtually". The term is a relative term, which is not defined in the specification. Because the specification does not provide a standard for ascertaining the degree to which the antibodies are required to be identical, recitation of the phrase renders the claim indefinite. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending the claim to delete the term "virtually" in line 2 can obviate this rejection.

Claim 8 is indefinite because the claim recites the term "corresponding counterpart". Recitation of the term renders the claim indefinite because it is not

clear to which counterpart the claim refers and also it is unclear how and to what extent the claim requires the counterparts of the antibodies to correspond. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 9 is indefinite because the claim recites the phrase "a protein binding molecule binding to Nup88". Recitation of the phrase renders the claim indefinite because it is unclear if the claim requires the protein-binding molecule to be bound to Nup88 or to be capable of binding Nup88. Furthermore, if the latter, it is unclear if the protein-binding molecule is required to bind specifically to Nup88 or merely non-specifically. Finally, it is unclear if the claim is meant to encompass a ligand of Nup88, which binds Nup88, or only an antibody or an antigen-binding fragment thereof. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 10 is indefinite because the claim recites the phrase "a nucleic acid binding molecule binding to the transcript of Nup88". Recitation of the phrase renders the claim indefinite because it is unclear if the claim requires the protein-binding molecule to be bound to Nup88 or to be capable of binding Nup88. Furthermore, if the latter, it is unclear if the protein-binding molecule is required to bind specifically to Nup88 or merely non-specifically. Finally, it is unclear if the claim is meant to encompass any molecule that binds the transcript of Nup88 or only a complementary nucleic acid molecule that hybridizes to the transcript. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Conclusion

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone

number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 17, 2001